REMARKS

Claims 1-8, 10, 11, 42-46, and 57 are pending in the instant application. Claims 1-3 and 11 have been amended without prejudice to their refiling as originally filed or as previously amended in future continuation or divisional applications. Claim 57 has been added; support for this claim may be found throughout the specification, for example at page 3, lines 14-26. Support for the amendments to the claims can be found throughout the specification, for example at page 21, lines 24-25, page 23, lines 22-23, and page 24, lines 9-15. No new matter has been added as a result of the above-described amendments. The rejections set forth in the Office Action have been overcome by amendment or are traversed by argument below.

1. Claim Rejections – 35 U.S.C. § 112, first paragraph

(A) The Office Action maintains a rejection of claims 2-8, 10, 11, and 42-46 under 35 U.S.C. § 112, first paragraph, as not being described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Specifically, the Office Action states that the issue is the breadth of the claims in light of the predictability of the art as determined by the number of working examples, the skill level of the artisan, and the guidance presented in the specification and in the prior art.

Applicants note that the written description requirement for a claimed genus "***may be*** satisfied through sufficient description of a representative number of species by actual reduction to practice... ***or*** by disclosure of the relevant, identifying characteristics ... sufficient to show the applicant was in possession of the claimed genus." (Emphasis added). MPEP 2163(II)(A)(3)(a)(ii). Applicants contend that the instant application, in combination with the knowledge already possessed by of one of skill in the art, does in fact disclose such relevant, identifying characteristics.

The claims as amended include explicitly-disclosed SEQ ID NO: 1 and fragments thereof (or polynucleotides encoding SEQ ID NO: 2 and fragments thereof), polynucleotides that hybridize to the complement of these nucleotide sequences under hybridization conditions allowing no more than a 21% mismatch between the nucleotide sequences, polynucleotides encoding conservatively substituted variants of SEQ ID NO: 2, and complementary sequences. The instant application explicitly teaches the nucleotide sequence and corresponding amino acid sequence for both the

human and murine IL-1ra-L polypeptide, as well as two splice variants of the human sequence. The specification specifically discloses these sequences, identified by SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6; SEQ NO: 35, and SEQ ID NO: 36, and inherently discloses fragments thereof – as fragments are merely portions of the specifically disclosed full-length sequences. Moreover, the specification positively recites that fragments of the disclosed sequences are encompassed within the scope of the invention. The specification also teaches nucleic acid fragments that hybridize to these sequences and provides a definition of moderately stringent conditions, as well as examples of such conditions.

In addition, the instant application teaches that conservative amino acid substitutions will produce a polypeptide having functional and chemical characteristics similar to those of IL-1ra-L polypeptides (page 24, line 30 to page 25, line 2) and that one of skill in the art will be able to determine suitable, particular variants of SEQ ID NO: 2 using well-known techniques (page 28, lines 2-4). The application further discloses many of these well-known techniques (*e.g.*, at page 28, line 4 thru page 30, line 15). Furthermore, one of skill in the art would be expected to utilize teachings outside of the specification and known to those of ordinary skill in the art in determining suitable variants of SEQ ID NO: 2. Applicants enclose herewith as Exhibit 1 various exemplary references, available at the time of filing of the instant application, that one of skill in the art would likely utilize in determining suitable variants of SEQ ID NO: 2. As discussed in Evans, there have been several studies mapping receptor-binding sites of IL-1 family members by site-directed mutagenesis (*J. Biol. Chem.* 270(19):11477, 1995). Additionally, the crystal structure of IL-1 receptor complexed with IL-1 beta has been deduced (Vigers *et al.*, 1997, *Nature* 386:190), as has the crystal structure of IL-1 receptor complexed with IL-1ra (Schreuder *et al.*, 1997, *Nature* 386:194). It is axiomatic that a patent application need not disclose what is understood to those of ordinary skill in the art. *In re Myers*, 410 F.2d 420, 161 U.S.P.Q. 668 (C.C.P.A. 1969) One of skill in the art, using the teachings of the specification in combination with such techniques disclosed in the art, would be able to predict a structure for the IL-1ra-R polypeptides of the instant application and to deduce which residues specifically are important for receptor binding. Thus, one of skill in the art would recognize that conservative substitutions could be made throughout the explicity-disclosed, previously unknown, sequences, without adversely affecting function or chemical characteristics.

Furthermore, the Office Action states that the claims are overly broad for reciting "a nucleic acid encoding a polypeptide with at least one modification that is a conservative amino acid substitution" as such a recitation encompasses a nucleic acid encoding a polypeptide in which every single amino acid has been changed. Applicants have amended claim 3 to recite an upper limit to the number of modifications. Specifically, claim 3 recites "a nucleotide sequence encoding a polypeptide as set forth in SEQ ID NO: 2 with at least one modification that is a conservative amino acid substitution, C-terminal truncation, or N-terminal truncation, *wherein the encoded polypeptide is at least 70 percent identical to the polypeptide set forth in SEQ ID NO: 2* and comprises at least 25 amino acid residues..." Support for this amendment may be found throughout the specification, for example on page 21, lines 24-25 and on page 24, lines 9-15. Thus, the limit to the number of modifications is the maximal number of modifications whereby the encoded protein retains 70 percent, but no less, identity with the amino acid sequence of SEQ ID NO: 2. Furthermore, percent identity between two polypeptides may be easily discerned by one of skill in the art either manually or by using a number of readily available computer programs. Thus, amended claim 3 is not overly broad with respect to "at least one modification."

Applicants, believing that the rejection of the pending claims based on 35 U.S.C. §112, first paragraph, for lack of written description have been overcome by amendment or traversed by argument, respectfully request that this ground of rejection be withdrawn.

(B) The Office Action maintains a rejection of claims 2-8, 10, 11, and 42-46 under 35 U.S.C. § 112, first paragraph, as not enabling. Applicants respectfully traverse. Independent claims 2 and 3 recite explicitly-disclosed SEQ ID NO: 1 and fragments thereof (or polynucleotides encoding SEQ ID NO: 2 and fragments thereof), polynucleotides that hybridize to the complement of these nucleotide sequences under hybridization conditions allowing no more than a 21% mismatch between the nucleotide sequences, polynucleotides encoding conservatively substituted variants of SEQ ID NO: 2, and complementary sequences. The specification specifically discloses both SEQ ID NO: 1 and SEQ ID NO: 2, and the specification is enabling for fragments of these sequences, as such fragments are merely portions of the specifically disclosed sequences.

Furthermore, as amended, the claims recite polynucleotides that hybridize to the complement of the claimed nucleotide sequences under hybridization conditions allowing no more than a 21% mismatch between the nucleotide sequences. One of skill in the art would be able to readily discern

(by simple inspection) whether there was a greater than 21% mismatch between two nucleic acid molecules. Furthermore, contrary to the assertion of the Office Action, the specification, on pages 24-30, does indeed provide adequate guidance as to the nature of the nucleic acid analogues or variants that may be constructed. The specification provides one of skill in the art with guidelines for preparing a polypeptide having one or more conservative substitutions (and thus the polynucleotide encoding such a polypeptide) that retains the functional and chemical characteristics of the IL-1ra-L polypeptides. The specification provides exemplary conservative amino acid substitutions (Table 1, pages 27-28), and teaches that amino acid substitutions may be made within a class of side chains (page 15, line 20), further considering the hydropathic (page 26, line 3) or hydrophilic (page 26, line 19) indices of amino acids. With respect to selection of specific amino acids, one of skill in the art may compare similar sequences within a species or from species to species (page 28, line 6) to identify regions likely to sustain alterations in amino acid sequence while maintaining functional and chemical characteristics. Additionally, one of skill in the art may analyze structure-function studies (page 29, line 1) or three-dimensional structures (page 29, line 8) in predicting which amino acid residues are important for activity or structure. Thus, Applicants contend that the determination of IL-1ra-R variants having conservative substitutions, or C- and/or N-terminal truncations is well within the skill of one of ordinary skill in the art through the practice of nothing more that routine experimentation.

Applicants, believing that the rejection of the pending claims based on 35 U.S.C. §112, first paragraph, for lack of enablement has been overcome by amendment or traversed by argument, respectfully request that this ground of rejection be withdrawn.

2. Claim Rejections – 35 U.S.C. § 112, second paragraph

(A) The Office Action maintains a rejection of claims 1-8, 10, 11, and 42-46 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicants regard as the invention. The Office Action states that the definition of moderately stringent conditions is "exemplary" and therefore remains vague and indefinite.

In response, Applicants have amended claims 1-3 to recite nucleic acid molecules having a nucleotide sequence that "that hybridizes to the complement of the nucleotide sequence [of a

previously recited nucleic acid molecule] under hybridization conditions allowing no more than a 21% mismatch between the nucleotide sequences." Support for the amendments can be found on page 23, lines 22-23. The claims, as amended, provide for a specific level of hybridization, and therefore, Applicants contend that the claims cannot be indefinite.

(B) The Office Action further maintains a rejection of claims 2-8, 10, 11, and 42-46 under 35 U.S.C. § 112, second paragraph, as being indefinite for reciting "has an activity of the polypeptide set forth in SEQ ID NO: 2." In response, Applicants have amended claims 2 and 3 to no longer recite "has an activity of." Thus the claims, as amended, can no longer be considered to be unclear as to which activity they refer.

(C) The Office Action further maintains a rejection of claim 46 under 35 U.S.C. § 112, second paragraph, as being vague and indefinite because the metes and bounds of the term "fragment" are unclear. Applicants respectfully traverse. The term "fragment" with respect to polypeptides is well-known in the art; one of ordinary skill in the art would find the term "fragment" to be definite in meaning any sub-sequence of the original sequence having fewer amino acids than the original sequence. Nevertheless, solely in order to expedite prosecution of the instant application, Applicants have amended claim 46 so that it no longer recites the term "fragment." Applicants contend that the amendment in no way limits the scope of the pending claims.

Applicants, believing that the rejection of the pending claims based on 35 U.S.C. §112 second paragraph, for indefiniteness has been overcome by amendment or traversed by argument, and respectfully ask the Examiner to withdraw this ground of rejection.

3. Claim Rejections – 35 U.S.C. § 102

(A) The Office Action maintains a rejection of claims 1-8, 10, 11, and 42-46, under 35 U.S.C. § 102(a), as being anticipated by International Publication No. WO 99/37662 (published July 29, 1999), contending that this reference discloses a nucleotide sequence that would be capable of hybridizing under moderately stringent conditions to the complement of the nucleotide sequence of SEQ ID NO: 1. Applicants respectfully traverse this rejection.

Applicants first note that the cDNA molecule disclosed in International Publication No. WO 99/37662 shares a sequence identity of only 32.4% with the nucleotide sequence of SEQ ID NO: 1 (*see* Exhibit A of Applicants' previous response). As amended, the claims recite a nucleic acid

molecule "that hybridizes to the complement of the nucleotide sequence ... under hybridization conditions allowing no more than a 21% mismatch between the nucleotide sequences." It is quite apparent that a sequence having 32.4% identity with SEQ ID NO: 1 would possess greater than a 21% mismatch between nucleotide sequences, and therefore would *not* hybridize to the nucleotide sequence of SEQ ID NO: 1 under the claimed conditions. Applicants thus respectfully submit that International Publication No. WO 99/37662 does not disclose a nucleic acid falling within the scope of the claims as amended, and ask the Examiner to withdraw this ground of rejection.

(B) The Office Action also maintains a rejection of claims 1-8, 10, 11, and 42-46, under 35 U.S.C. § 102(b), as being anticipated by European Patent Application No. EP 0 855 404 (published July 29, 1998), contending that this reference discloses a nucleotide sequence that would be capable of hybridizing under moderately stringent conditions to the complement of the nucleotide sequence of SEQ ID NO: 1. Applicants respectfully traverse this rejection.

Applicants first note that the cDNA molecule disclosed in European Patent Application No. EP 0 855 404 shares a sequence identity of only 50.9% with the nucleotide sequence of SEQ ID NO: 1 (*see* Exhibit B of Applicants' previous response). As amended, the claims recite a nucleic acid molecule "that hybridizes to the complement of the nucleotide sequence ... under hybridization conditions allowing no more than a 21% mismatch between the nucleotide sequences." It is quite apparent that a sequence having 50.9% identity with SEQ ID NO: 1 would possess greater than a 21% mismatch between nucleotide sequences, and therefore would *not* hybridize to the nucleotide sequence of SEQ ID NO: 1 under the claimed conditions. Applicants thus respectfully submit that European Patent Application No. EP 0 855 404 does not disclose a nucleic acid falling within the scope of the claims as amended, and ask the Examiner to withdraw this ground of rejection.

(C) The Office Action also maintains a rejection of claims 1-8, 10, 11, and 42-46, under 35 U.S.C. § 102(b), as being anticipated by U.S. Patent No. 5,075,222 (issued December 24, 1991), contending that this reference discloses a nucleotide sequence that would be capable of hybridizing under moderately stringent conditions to the complement of the nucleotide sequence of SEQ ID NO: 1. Applicants respectfully traverse this rejection.

Applicants first note that the cDNA molecule disclosed in U.S. Patent No. 5,075,222 shares a sequence identity of only 28.8% with the nucleotide sequence of SEQ ID NO: 1 (*see* Exhibit D of Applicants' previous response). As amended, the claims recite a nucleic acid molecule "that

hybridizes to the complement of the nucleotide sequence ... under hybridization conditions allowing no more than a 21% mismatch between the nucleotide sequences." It is quite apparent that a sequence having 28.8% identity with SEQ ID NO: 1 would possess greater than a 21% mismatch between nucleotide sequences, and therefore would *not* hybridize to the nucleotide sequence of SEQ ID NO: 1 under the claimed conditions. Applicants thus respectfully submit that U.S. Patent No. 5,075,222 does not disclose a nucleic acid falling within the scope of the claims as amended, and ask the Examiner to withdraw this ground of rejection.

Applicants respectfully contend that the rejections based on 35 U.S.C. § 102 have been overcome by amendment or traversed by argument, and request that the Examiner withdraw all rejections made on this basis.

CONCLUSIONS

Applicants respectfully contend that all conditions of patentability are met in the pending claims as amended and therefore respectfully request allowance.

If Examiner Mertz believes it to be helpful, she is invited to contact the undersigned representative by telephone at (312) 913-0001.

Respectfully submitted,
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